



PATENT
Attorney Docket No. 019496-006210US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of:

CHOO, Yen

Application No.: 09/424,482

Filed: February 29, 2000

For: NUCLEIC ACID BINDING
POLYPEPTIDE LIBRARY

Examiner: Teresa D. Wessendorf

Art Unit: 1639

APPELLANT'S BRIEF UNDER 37 CFR
§1.192

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By Kristi Coplin
Kristi Coplin

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Sir:

REAL PARTY IN INTEREST:

Gendaq Ltd., a wholly owned subsidiary of Sangamo Biosciences, Inc.

RELATED APPEALS AND INTERFERENCES:

None.

STATUS OF CLAIMS:

Claims 1, 2, 4-8 and 10-28 are pending. Claims 4, 5, 8 and 10-25 are withdrawn.
Claims 1, 2, 6-7 and 26-28 are rejected. All rejected claims are appealed. The claims are listed in Appendix A.

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STATUS OF AMENDMENTS:

A final office action was mailed June 18, 2003. An amendment after final is filed herewith. The amendment after final makes minor amendments to claims 26-28 that eliminate certain issues raised by the Examiner under 35 USC 112, second paragraph and also corrects a minor typographic error in claim 1. The listing of claims assumes the amendment after final will be entered although this has not yet been determined.

SUMMARY OF THE PRESENTLY CLAIMED INVENTION:

The present claims are directed to libraries of zinc finger proteins in which certain positions of adjacent zinc fingers are at least partially randomized. Claim 1 specifies a zinc finger polypeptide library in which each polypeptide comprises more than one zinc finger. Amino acids within each zinc finger protein are assigned numbers from -1 to +9 in accordance with convention whereby position +1 is the first residue of an alpha helix (specification at p. 7, lines 5-9). Each polypeptide member of the library is at least partially randomized such that randomization extends to cover at least one position in each of adjacent fingers (see, e.g., specification at p. 8, lines 16-22). The position is selected from the group consisting of -1, 1, 2, 3, 5 and 6 in a one adjacent finger, and -1, 1, 2 and 3 in the other (specification at p. 9, lines 16-18).

Claim 26 specifies a preferred embodiment in which the randomization extends to at least position 6 of one finger and position 2 of an adjacent finger. Because these residues contact the same base pair of a target, it is advantageous they be varied together (specification at p. 9, lines 5-9). Claim 27 specifies particularly preferred embodiment in which randomization occurs at positions -1, 1, 2, 3, 5 and 6 of a first finger and -1, 1, 2 and 3 of a second finger. Claim 28 specifies another particularly preferred embodiment in which randomization occurs at positions 3, 5 and 6 of a first zinc finger and -1, 1, 2 and 3 of a second zinc finger (specification at p. 9, lines 16-22).

The present application provides the insight that by simultaneously randomizing adjacent fingers, one can obtain zinc finger proteins with additional binding specificities compared to zinc finger proteins obtained by previous methods (compare specification at p. 2, lines 12-27 (discussing prior art) and p. 36, lines 20-29, discussing results obtained with the presently claimed invention). The additional specificities result because of binding interactions

between adjacent fingers, and randomization of residues from both fingers is needed to encompass the full range of binding specificities.

ISSUES:

1. Whether claims 1-2, 6-7 and 26-28 have a utility as required by 35 USC 101.
2. Whether the specification describes a utility for claims 1-2, 6-7 and 26-28 as required by 35 USC 112, first paragraph.
3. Whether claims 1-2, 6-7 and 26-28 comply with the written description requirement of 35 USC 112, first paragraph.
4. Whether claims 1-2 and 6-7 are indefinite under 35 USC 112, second paragraph.
5. Whether claims 1-2, 6-7 and 26-28 would have been obvious under 35 USC 103(a) over any one of Greisman et al., US 6,420,248 (Greisman), Rebar et al., US 5,789,538 (Rebar) or Wu et al. PNAS 92, 344-348 (1995) (Wu).
6. Whether claims 1-2, 6-7 and 26-28 would have been obvious under 35 USC 103(a) over Choo et al., Current Opinion in Biotechnology 6, 431-436 (1995) (Choo II).
7. Whether claims 1-2, 6-7 and 26-28 would have been obvious over claims 1 and 2 of Choo et al., US 6,007,998 (Choo I) under the obviousness-type double patenting doctrine.

GROUPING OF THE CLAIMS:

The rejected claims do not stand or fall together. As can be seen from the statement of issues, different rejections have been applied to different claims. Also, certain dependent claims are patentable on additional grounds discussed in more detail below.

ARGUMENT

Issue 1: Claims 1-2, 6-7 and 26-28 Have Utility as Required by 35 USC 101

The claims stand rejected as not supported by a specific asserted or a well-established utility. The Examiner says that the claims are drawn to libraries not compounds. The Examiner also says that the Examples do not illustrate uses of compounds (see office action of December 20, 2002 at p. 5).

A "specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter unless there is reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 183 USPQ 288 at 297 (CCPA 1974) (emphasis in the original). Here, the specification expressly discloses that the claimed libraries can be screened to isolate individual zinc finger proteins having at least three utilities including diagnostics, research tools and therapeutics (see pp. 27-32). Any of these utilities is credible given the nature and mechanism of zinc finger proteins and the state of the art. Zinc finger proteins are proteins that bind specific DNA target sequences to modulate the expression of a gene. Other reagents that perform similar functions (e.g., DNA probes and antisense RNAs) are well known to be useful for such purposes. There is no reason to think that a zinc finger protein that binds a specific sequence would be less useful than a DNA probe that binds the same sequence, or that a zinc finger that modulates a gene would be less useful than an anti-sense RNA that modulates the same gene. Because the asserted utilities are credible for reagents such as probes and antisense RNA having analogous functions to zinc finger proteins, they are credible for zinc finger proteins too.

Although the Examples in the specification may focus on isolation of zinc finger proteins with a given binding specificity rather than illustrating uses of zinc finger proteins, the latter readily follows from the former. For example, if one has a zinc finger protein that can bind to a given target sequence, it is not difficult to see how the zinc finger protein can be used in a diagnostic assay for detecting that target sequence. The underlying principles are the same as in any other detection assay, namely, one contacts a target with a zinc finger protein, and determines whether specific binding occurs.

In the final office action, the Examiner disagreed with the above explanation on a number of grounds which will be addressed in turn. Many of the Examiner's comments are based on the incorrect assumption that one must use the entire library en masse rather than individual zinc finger proteins having a defined binding specificity selected from the library. It is clear that the specification discloses selecting individual zinc finger proteins from the library and using these as research, diagnostic or therapeutic reagents (see specification at, e.g., paragraph bridging pp. 5-6).

Second, the Examiner cites *Brenner vs. Manson*, 148 USPQ 689 (S.Ct. 1966) for the proposition that patentability cannot be based on a utility as a research tool. However, such an interpretation is contrary to MPEP 2107.01 which provides that "many research tools" have "clear, specific and unquestionable utility." Thus, *Brenner* does not stand for the general proposition that patentable utility can never be based on utility a research tool. In *Brenner*, the issue was the utility of a method of producing a chemical compound when the compound had no credible utility other than to allow research to be conducted on the compound to discover such a utility.

The facts and circumstances here are different from those in *Brenner*. Here, it is known that the zinc finger proteins of the claimed library have the property of sequence-specific binding to a target sequence. The Examples of the application also demonstrate that the libraries can routinely be screened using phage display techniques to isolate particular zinc finger proteins with specificity for particular target sequences. As discussed above, when one has a zinc finger protein with specificity for a particular target sequence, a variety of applications relating to detecting the target sequence or modulating its expression readily follow. Thus, in contrast to the compound in *Brenner*, zinc finger proteins that result from routine screening of the claimed libraries have several credible utilities as diagnostics, therapeutics and/or research tools.

Moreover, with respect to one of these utilities, that of zinc finger proteins as research tools, this utility is of a different nature than the research found unacceptable in *Brenner*. In *Brenner*, the subject of research was the very compound that would result from the claimed method. Here, the zinc finger proteins that result from screening the claimed libraries are used as tools to conduct research on other subjects (for example, the effects of suppressing expression of a gene, see specification at p. 29, lines 18-19). In this respect, the zinc finger proteins are analogous to other laboratory reagents or equipment, such as restriction enzymes or a gas chromatograph which unquestionably have patentable utility. Therefore, *Brenner* does not preclude utility based on zinc finger proteins as research tools to conduct research on other subjects. Moreover, as discussed above, the zinc finger proteins that result from screening the claimed libraries also have utility as diagnostic or therapeutic reagents.

The Examiner also criticizes the cited diagnostic, therapeutic or research utilities as being general utilities, and even says that appellants have admitted as such. However, the

Examiner has taken appellants' words out of context. These utilities are general only in the sense that they are generally applicable to zinc finger proteins that can be screened from the claimed libraries. Different zinc finger proteins screened from within the libraries have different binding specificities and are used for different purposes. For example, a zinc finger protein selected to bind to a HIV nucleic acid sequence (specification at p. 29, line 24) has different applications than a zinc finger protein selected to bind to ras (specification at p. 29, lines 20). Thus, the claimed zinc finger protein libraries can be used to select individual zinc finger proteins that have specific diagnostic, research and/or therapeutic uses.

Therefore, there is no reason to doubt that the utilities described by the specification are specific and credible and the rejection should be reversed.

Issue 2: The Specification Describes a Utility for Claims 1-2, 6-7 and 26-28 as Required by 35 USC 112, First Paragraph

The rejection is based on the allegation that the claimed invention is not supported by a utility as discussed under Issue 1 (final office action at p. 7). This rejection therefore raises the same underlying issue as Issue 1 and appellants respond as above.

Issue 3: Claims 1-2, 6-7 and 26-28 Comply with the Written Description Requirement of 35 USC 112, First Paragraph

The final office action alleges that the specification does not provide a description of a "first and second adjacent finger of an alpha helix" (at p.8).

Initially, it is noted that the above phrase is not used in the claims. The phrase appears to suggest that first and second fingers are components of the same alpha helix, but this is not what the claims say. Rather, the claims define a library of polypeptides in which each polypeptide comprises more than one zinc finger. The amino acid positions in the zinc finger are defined by reference to the alpha helix within that finger. Because the polypeptides have more than one finger, it follows that they have more than one alpha helix, one for each zinc finger.

In the event that the Examiner is alleging more generally that the reference to "first and second adjacent fingers" in claim 1 lacks written description, it is noted that explicit support is provided by e.g., original claim 3 of the application as filed, which is directed to a

library in which each polypeptide comprises more than one zinc finger which has been at least partially randomized, "wherein the randomized zinc fingers are adjacent." Additional support is provided by p. 9 of the specification and Fig. 6 providing examples of how to randomize adjacent fingers. For example, p. 9, lines 10-15 describes randomization of a zinc finger protein comprising zinc fingers F1, F2 and F3. As shown in Fig. 6, the fingers are arranged in numerical order so that F1 and F2 are adjacent and F2 and F3 are adjacent. The specification describes one library in which F1 and F2 are randomized and another library in which F2 and F3 are randomized (p. 9, lines 10-15). Thus, in each library two adjacent fingers are randomized. The next paragraph discloses randomizing positions selected from -1, 1, 2, 3, 5 and 6 in a first zinc finger and -1, 1, 2 and 3 in a second zinc finger. Because the specification first describes randomizing a pair of adjacent fingers, and then lists the respective positions for randomization in two fingers, it would be understood that these are the positions to be used in the randomization of the adjacent fingers. For these reasons, it is submitted that the claims satisfy the written description requirement of 35 USC 112, first paragraph and the rejection should be reversed.

Issue 4: Claims 1-2 and 6-7 are Not Indefinite under 35 USC 112, Second Paragraph

Claim 26 stands rejected on the basis that the claim should recite a library rather than a method. Appellants agree and have corrected this error in the accompanying amendment after final.

Claims 27 is said to be unclear in reciting 'at least' positions -1, 1, 2, 3, 5, 6 of a first zinc finger and -1, 2, 2, and 3 of a second finger. The Examiner says that it is not clear what other positions can be randomized. The Examiner also says the claim is inconsistent with claims 1 recitation that at least one of the positions is randomized.

To reduce the issues for an appeal, applicants have amended claim 27 (and also claim 28 which contains analogous language) to delete the term "at least." However, appellants do not agree with the rejection and offer the following comments if the Examiner refuses to enter the amendment after final.

Claim 27 is not inconsistent with claim 1. Claim 1 requires at least one of the designated positions to be randomized and does not exclude randomization of other

nondesignated positions. Claim 27 requires all of the designated positions to be randomized and likewise does not exclude randomization of other nondesignated positions. Thus, claim 27 imposes an additional limitation within the scope of claim 1.

That claim 27 is open to randomization at positions besides those designated in the claim does not mean the claim is indefinite. The primary purpose of § 112, second paragraph, is to apprise the public as to what constitutes infringement. Another purpose of the requirement is to provide a clear measure of the invention in order to facilitate determinations of patentability. *United Carbon Co. v. Binney Co.*, 317 U.S. 228, 236 (1942). Here, one can readily determine prior art or assess infringement from whether the prior art or infringing product has substitutions at all of the designated positions. It is immaterial to such an analysis whether the prior art or infringing product does or does not have additional positions of randomization because the claim neither requires nor excludes them. For these reasons, it is submitted the claim is not indefinite.

The Examiner alleges that claim 1 is indefinite in its recitation of "at least partially randomized such that the randomization extends to cover at least one position." This rejection appears to raise essentially the same issue as discussed under claim 27. This phrase is not indefinite because it leaves the zinc fingers specified in the claim open to randomization at other than one of the designated positions. Claim 1 requires randomization of at least one of a Markush group of positions, and is open to randomization at other positions not within the group. Again, there is no difficulty in applying the prior art or determining infringement of such claim. Accordingly, the claim is not indefinite.

The Examiner also alleges that claim 1 is indefinite as to what constitutes an adjacent finger in a helix. As discussed in connection with the rejection under 35 USC 112, first paragraph, the claim does not refer to adjacent fingers within a helix. Rather, the claim refers to adjacent zinc fingers, each of which has its own helix. Such is illustrated by Figure 1 of the application which shows a protein with three zinc fingers, each of which has its own helix. Insofar as the rejection can be understood in light of the actual claim language used, the claim is not indefinite.

Issue 5: Claims 1-2, 6-7 and 26-28 Would Not Have Been Obvious under 35 USC 103(a) over any one of Greisman, Rebar or Wu

1. The Examiner's rationale

The Examiner states that each reference identifies positions -1, 1, 2, 3, 5 and 6 as being critical residues for binding and randomizes these residues in a single finger (final office action at p.13). The Examiner takes the view that the references suggest randomization of a second finger based on the target subsites to which the fingers bind (at p. 13). The Examiner further takes the view that it would have been obvious to choose which positions to randomize in the second finger (final office action at pp. 13-14).

2. The cited references

Wu discusses a method of isolating a three-finger zinc finger protein that binds to a desired target site. In this method, three randomized libraries, one for each finger were independently constructed (p. 345, second column, 2nd paragraph). Each randomized finger was joined to two wildtype fingers of a natural zinc finger protein for screening (p. 346, first column, first paragraph). Each library was independently selected (see Table 1 at p. 346). Wu proposes that selected fingers from each of the three libraries be linked in a modular fashion to generate a new zinc finger protein (p. 348, first column, 3rd paragraph). Wu also explains the rationale for independent selection of each zinc finger. That is, Wu teaches that library size constrains complete randomization to six positions (p. 345, column 2, paragraph 2). The artisan would infer from Wu that simultaneous complete randomization of all fingers at all possible positions affecting binding specificity would exceed the capacity of the phage display system.

Rebar discusses a similar procedure to Wu. Again, each of the three fingers in a zinc finger protein is randomized independently and the selected fingers are rejoined in a modular fashion after selection (see col. 8, lines 24-28).

Greisman¹ discusses a more elaborate strategy than Rebar and Wu for selecting zinc finger proteins. The strategy still involves randomizing and selecting one finger at a time (see col. 5, lines 37-40). However, Greisman's method is performed in an iterative fashion in which finger(s) that have previously been selected provide context for selection of another finger (see claim 1). In brief, in a first step, a zinc finger protein comprising one randomized finger and two constant fingers is selected. In a second step, a second zinc finger protein comprising one randomized finger, one previously selected finger, and one constant finger is selected. In a third step, a zinc finger protein comprising one randomized finger and two previously selected fingers is selected. The iterative method of selection, although more elaborate, has the advantage that new fingers are selected in a relevant structural context (col. 6, lines 66-67).

3. The Cited Art Distinguished

Each of the three cited references differs from the present claims in not describing a library of zinc finger proteins in which at least two fingers (much less two adjacent fingers) of the proteins have been simultaneously randomized. The cited references take a different approach in providing libraries in which only one finger of a zinc finger protein is randomized. After separate selection of each finger, the fingers are joined in a modular fashion to form a zinc finger protein that binds to a desired target sequence.

"Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." *In re Geiger*, 2 USPQ2d 1276 (Fed. Cir. 1987). The motivation must have sufficient "force" to "impel persons skilled in the art to do what applicant has done." *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (BPAI 1993).

The only motivation proposed by the Examiner for modifying the teaching of the references is "Each of these regions [sic, references?] suggests randomization of the second finger based on the subsites to which these fingers bind" (Final office action at p. 13, 3rd

¹ The cited Greisman reference, US 6,410,248 B1, has a 35 USC 102(e) prior art date of January 30, 1998, after the priority date of the present application, which is May 23, 1997. Nevertheless, it is noted that an earlier Greisman publication of substantially similar content, Greisman and Pabo, A General Strategy for Selecting High-Affinity Zinc Finger Proteins for Diverse DNA Target Sites, *Science*, 275:657-661 (Jan. 31, 1997) is citable under 35 USC 102(a). Thus, appellants address the merits of the rejection.

paragraph). It is assumed that the Examiner means that the length of target sequence contemplated by the references requires a zinc finger protein having more than one selected finger. However, a goal of producing a zinc finger protein having more than one selected finger does not suggest producing a library of zinc finger proteins in which more than one zinc finger has been simultaneously randomized. As shown in the references, zinc finger proteins having more than one selected finger can be obtained by individually selecting each finger and then combining the selected fingers. Therefore, the motivation asserted by the Examiner does not suggest deviating from the teaching of the references.

The motivation asserted by the Examiner is inconsistent with disclosure in Wu teaching away from the claimed invention. A reference teaching away from an invention is strong evidence of non-obviousness, in fact, the very antithesis of obviousness, to which a rebuttal should not even be required. *In re Buehler*, 185 USPQ 781 (CCPA 1975); *In re Hedges*, USPQ 685, 687 (Fed. Cir. 1986). As discussed above, Wu indicates that the capacity of the phage display method is limited to complete randomization of about six positions. As the Examiner has noted, there at least six positions that may affect binding in a single zinc finger. Thus, fully randomizing every position that might affect binding in two zinc fingers would exceed the capacity of the phage display system. The constraints imposed by the capacity of the phage display method would motivate the artisan away from departing from the practice of the Wu reference (and Rebar and Greisman) in randomizing one finger at a time.

The motivation asserted by the Examiner is also inconsistent with case law holding that if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 123 USPQ 349 (CCPA 1959). Here, the proposed modification of Greisman is inconsistent with the principle of operation of Greisman's method. As discussed above, Greisman, like Rebar and Wu, optimizes zinc fingers one at a time. However, whereas Rebar and Wu optimize each finger independently, Greisman performs an iterative process in which the second finger to be optimized is optimized in the context of the first selected finger, and the third finger to be optimized is optimized in the context of the first and second selected fingers. This elaborate iterative scheme of optimizing successive fingers in the context of previously selected fingers

would be redundant if one could simply optimize all of the fingers together. Thus, the motivation proposed by the Examiner is inconsistent with the principle of operation of Greisman's method.

For these reasons, the Examiner has not established motivation sufficient to impel the artisan to change the teaching of any of the cited references, and rejection should be reversed.

Claim 26 is distinguished on additional grounds. This claim specifies that at least position +6 is randomized in a first finger and at least position +2 in a second adjacent finger. As indicated in the Summary of the Presently Claimed Invention randomizing this combination of positions is advantageous because the amino acids occupying these respective positions in adjacent zinc fingers bind to the same base pair of a target sequence. The cited art does not teach randomization of this combination of amino acids in adjacent fingers.

As discussed in connection with Wu, the number of positions that may affect binding is too large to fully randomize each position in more than one zinc finger. Therefore, assuming *arguendo* one were to attempt simultaneous randomization of more than one zinc finger at all, one would have to consider selecting a subset of positions for randomization from all of those that might affect binding. The cited art does not provide any suggestion to select position +6 from one finger in combination with position +2 from an adjacent finger.

Claims 27 and 28 are distinguished for similar reasons to claim 26. These claims specify particular combinations of amino acid positions in adjacent first and second fingers for randomization. The combinations recited in claims 27 and 28 both include the preferred +6/+2 combination recited in claim 26. The cited art does not suggest selecting the combinations of positions recited in claims 27 and claims 28 from all of the positions that could affect binding specificity in both fingers.

Issue 6: Claims 1-2, 6-7 and 26-28 Would Not Have Been Obvious under 35 USC 103(a) over Choo II²

In the first office action, mailed December 20, 2002, the Examiner did not explicitly set forth a case of obviousness based on Choo II but simply said the teaching was the

² Applicants use the same nomenclature (Choo II and Choo I) as used for the same reference previously in prosecution even though in the present brief Choo II is discussed before Choo I.

same as Choo I (see below) and that the combination of Choo II, Ogata, PNAS 89, 6428-6432 (1992) (Ogata) and Hall, Cell Growth and Differentiation 3, 207-216 (1992) (Hall) rendered the claimed invention obvious (office action of December 20, 2002 at p. 11). In the present office action, Choo II is apparently applied on its own without Ogata and Hall. The Examiner does not indicate explicitly what parts of Choo II are relied on for a *prima facie* case of obviousness. Rather the Examiner simply responds to previous comments of appellants regarding certain teaching away evidence in Choo II. Thus, the precise nature of what the Examiner is relying on in Choo II, and the alleged motivation for modifying the teaching of Choo II are unclear.

Choo II is a review article that considers strategies for design of new proteins made of zinc fingers. The reference asks the question of how phage display technology can be used in the design of whole DNA-binding domains containing multiple zinc fingers. The reference first considers what might appear as the "most obvious strategy" of simultaneously randomizing each finger in a multifinger protein. However, the reference rejects this strategy as being "unlikely to be practical in the near future" (p. 433 paragraph bridging columns). The reason the strategy is unlikely to be practical is library size (see p. 433, second column, lines 1-3, the same concern discussed by Wu (see above). The reference continues "[M]ore practicable approaches are at hand because , availing ourselves of the modular nature of zinc fingers, we can assemble a DNA-binding domain from appropriate combinations of individually selected fingers" (at p. 433, second column, second paragraph).

In brief, the modular strategy discussed in Choo II involves the same underlying principle of randomizing one zinc finger at a time as discussed by Wu, Rebar and Greisman. The claimed invention is distinguished over Choo II for the same reasons as Wu Rebar and Greisman. In addition, Choo II, like Wu, teach away from the claimed invention by stating that simultaneously randomizing each of three zinc fingers in a three-finger zinc finger protein is "unlikely to be practical in the near future" due to the large number of permutations (p. 433, paragraph bridging cols. 1 and 2).

The Examiner disagrees with the above analysis on the basis that Choo II's reference to "more practicable approaches" of assembling a DNA binding domain from "appropriate combinations of individually selected fingers" provides a remedy for the teaching away evidence (final office action at p. 15, first paragraph, emphasis in the original). However,

the Examiner apparently overlooks the fact that Choo II's proposed remedy is not the claimed invention. Rather the proposed remedy is individually selected fingers as in any of Wu, Rebar or Greissman. Thus, Choo II teaches away from simultaneously randomizing multiple zinc fingers and toward the approach described in any of the other cited references of assembling a zinc finger protein from individually selected fingers.

The Examiner also alleges that appellants' arguments are not commensurate with the claims in the claims do not have a randomizing step (final office action at p. 15). This is merely a matter of semantics. The claims require that each polypeptide of the libraries has been "at least partially randomized" in each of adjacent first and second zinc fingers. The partial randomization produces a distribution of polypeptides randomly differing from each other at the randomized sites. Therefore, the feature of partial randomization characterizes the polypeptides in the library not just the method used to produce the library.

Finally, the Examiner alleges that Choo II discloses at p. 433, col. 2 the "obvious strategy to simultaneously randomized [sic] each finger in a multifinger library." However, the Examiner omits to mention that the paragraph of Choo II concludes "this approach is unlikely to be practical in the near future." Thus, viewed in full context, the cited paragraph from Choo II teaches away from simultaneously randomizing each finger in a multifinger library.

For these reasons, it is submitted that the Examiner has not established motivation sufficient to impel the artisan to modify the teachings of Choo II to achieve the claimed invention.

Claims 26-28 are distinguished from Choo II on additional grounds for essentially the same reasons discussed in connection with Issue 5.

Issue 7: Claims 1-2, 6-7 and 26-28 Would Not Have Been Obvious over Claims 1 and 2 of Choo I under the Obviousness-Type Double Patenting Doctrine

The final office action states that the above rejection is based on reasons of record (at p. 16). However, the previous office action applied Choo I in combination with Ogata and Hall. The office action took the view that one would have been motivated to combine the teachings of the references for the benefit of obtaining "compounds with more or increased binding pharmacological effects or potency due to the high specificity action or binding" (office

action of March 20, 2003 at p.10). The precise basis on which the Examiner applies Choo I alone and motivation for altering the teaching of Choo I have not been articulated.

A double patenting rejection of the obviousness types is analogous to the nonobviousness requirement of 35 USC 103, except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 154 USPQ 29 (CCPA 1967). A double patenting rejection should therefore make clear the differences between the inventions defined by the conflicting claims and the reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent. MPEP 804B. 1.

Here, the claims of Choo I specify libraries of DNA encoding zinc finger polypeptides having at least one randomized zinc finger. The randomized finger has a random allocation of amino acids at certain specified positions (i.e., -1, +2, +3 and +6 and at least one of +1, +5, and +8). Although the claims are open to the possibility of a second randomized finger being present, they do not specify which positions are randomized in the second randomized finger. As discussed in connection with Choo II or Wu, it would not be obvious simply to substitute all the same positions in the second protein as the first due to constraints on the number of positions that can be fully randomized. The claims also do not disclose or suggest that if a second randomized finger is present it is adjacent to the first randomized finger, as required by the present claims.

In the first office action, the only motivation asserted by the Examiner for modifying the teaching of Choo I's claims was that of producing compounds with greater potency due to high specificity or binding. This motivation was asserted in the context of combining the teaching of Choo I with Ogata and Hall. The motivation is insufficient to support modification of Choo I either alone or with Ogata and Hall. “To establish a *prima facie* case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the *specific* combination that was made by the applicant.” *In re Dance*, 160 F.3d 1339, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis supplied). The motivation must be specific and objective. *In re Dembiczak*, 50 USPQ2d 1614 (Fed. Cir. 1999). The requirement for evidence of particularized motivation provides a safeguard against the “tempting but forbidden zone of hindsight.” *Dembiczak* at p.

1616. Here, the asserted motivation (producing compounds with greater potency due to high specificity or binding) is so general that it could be asserted with respect to virtually any references in the biomedical field. The motivation identifies only a general desiderata without pointing in the direction of any specific modifications of Choo I that are required to achieve the present claims. Further, the asserted motivation is not supported by an evidentiary source. The Examiner has not identified where the asserted motivation is found in the cited references or elsewhere. Absent the safeguards of either a specific motivation or an evidentiary source supporting the motivation, one cannot be assured that the combination of references was not the result of hindsight.

In the final office action, the Examiner's only additional comment is that "Choo positively discloses a partial randomized allocation of amino acids, the partially randomized zinc finger having a random allocation of amino acids at positions -1, +2, +3 and +6 and at least one of positions +1, +5 or +8" (final office action at p. 16). This comment does not address the issue of which amino acids to select in the second finger. As indicated above, it is was not obvious simply to randomize the same amino acids in the second finger due to constraints on library size. This comment also does not address motivation to randomize first and second *adjacent* fingers.

For these reasons, it is submitted that the Examiner has not established motivation sufficient to impel the artisan to modify the claims of Choo I to achieve the invention, and that the rejection should be reversed.

Claims 26-28 are distinguished on additional grounds from the claims of Choo I for essentially the same reasons as discussed in connection with Issue 5. That is, these claims are directed to randomization of specified combinations of amino acids in the first and second adjacent fingers. Although the claims of Choo I recite a number of positions for randomization in a first finger, they do not disclose which amino acids to select if a second finger is randomized. As discussed above, it was not obvious to select all of the same positions in the second finger as are randomized in the first finger. The claims of Choo I do not disclose or suggest selecting position +2 in the second finger, as required by claim 26, nor the sets of positions including +2 in the second finger required by claims 27 and 28

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CONCLUSION:

For the reasons discussed above, it is respectfully submitted the rejections should be reversed.

Please deduct the requisite fee, pursuant to 37 CFR § 1.17(c), of \$160 from deposit account 20-1430 and any additional fees associated with this Brief. This Brief is submitted in triplicate.

Respectfully submitted,



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**APPENDIX A:
APPEALED CLAIMS**

Claim 1. A zinc finger polypeptide library in which each polypeptide comprises more than one zinc finger comprising amino acid positions -1 to +9 with position 1 representing the first amino acid of an alpha-helix and wherein each polypeptide has been at least partially randomised such that the randomisation extends to cover at least one position selected from the group consisting of -1, 1, 2, 3, 5 and 6 and at least one position selected from the group consisting of -1, 1, 2 and 3 in first and second adjacent fingers respectively.

Claim 2. A library according to claim 1 wherein each polypeptide comprises between three and six zinc fingers.

Claim 6. A library according to claim 1, wherein the randomised positions are selected from positions -1, 1, 2, 3, 5 and 6.

Claim 7. A library according to claim 1, wherein the randomization of amino acid residues is restricted such that the following amino acids appear at the given positions:

Position	Amino Acids
-1	R, Q, H, N, D, A, T
1	S, R, K, N
2	D, A, R, Q, H, K, S, N
3	H, N, S, T, V, A, D
5	I, T, K
6	R, Q, V, A, E K, N, T

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Claim 26. The library of claim 1, wherein the randomization extends to at least positions 6 and 2 of the adjacent first and second zinc fingers respectively.

Claim 27. A library according to claim 1 wherein positions -1, 1, 2, 3, 5 and 6 of a first zinc finger and -1, 1, 2 and 3 of a second finger are randomized.

Claim 28. A library according to claim 1 wherein positions 3, 5 and 6 of a first zinc finger and -1, 1, 2 and 3 of a second finger are randomized.